

**RING OPENING OF THIOPHENE DERIVATIVES
AND RELATED STUDIES**

REGIO- AND STEREOCHEMICAL ASPECTS

Olle Karlsson



LUND 1982

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Title and subtitle

Ring Opening of Thiophene Derivatives and Related Studies.
Regio- and Stereochemical Aspects.

Abstract:

The rate of ring opening of a number of 3-lithio-cycloalkane[b]thiophenes has been determined and a number of cyclic thioenol ethers has been synthesized.

The total syntheses of two naturally occurring thioenynes from the genus *Anthemis* have been achieved starting from 2,4-dibromothiophene. The key step was the ring opening of 3-bromo-5-(1-propynyl)-2-trimethylsilylthiophene after halogen-metal exchange upon treatment with butyllithium.

The introduction of a trimethylsilyl group in the 2-position of 3-bromothiophenes and -selenophenes and its accelerating effect on the rate of ring opening of the corresponding 3-lithio derivatives are described.

The Vilsmeier-Haack reaction and enol acetate formation of some methyl-substituted cycloalkanones are discussed in view of the regiochemistry of the resulting β -chlorovinyl aldehydes and enol acetates. It was found that the isomers with the double bond distant from the methyl group are formed predominantly.

The formation of the isomeric 2-substituted 5,6-dihydro-4H-cyclopenta[b]thiophen-4-ones and 4,5-dihydro-6H-cyclopenta[b]thiophen-6-ones upon reaction of 2-substituted thiophenes with methacrylic acid in PPA is described.

Some acylthiophenes and -selenophenes were brominated in the aromatic ring by bromine in aqueous sodium acetate.

5-Alkyl-3-bromo-2-methylthiophene-1,1-dioxides were treated with phenyl- and alkylolithium compounds. Two competing ring-opening reactions yielded: (a) lithium enyne sulfinates via halogen-metal exchange and benzyl enyne sulfones after trapping with benzyl bromide, and (b) isomeric enynes via organolithium attack on the S-carbon and subsequent extrusion of sulfur dioxide and lithium bromide.

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Date Sept 29, 1982

This review is a summary of the following papers referred to as I-IX.

- I. T. Frejd, J.O. Karlsson and S. Gronowitz
Ring-opening reactions. 18. Synthesis of thioenol ethers.
J. Org. Chem. 46, 3132 (1981).
- II. T. Frejd and J.O. Karlsson
Rates of the ring opening of some bicyclic
3-thienyllithium derivatives.
Manuscript.
- III. S. Gronowitz, T. Frejd, J.O. Karlsson, K. Lawitz,
P. Pedaja and K. Pettersson
Ring-opening reactions. XIX. On the ring-opening of
2-silylated 3-thienyl- and -selenienyllithium
derivatives.
Chem. Scripta 18, 192 (1981).
- IV. J.O. Karlsson, S. Gronowitz and T. Frejd
Regio- and stereospecific synthesis of acetylenic
thio enol ethers occurring in the genus Anthemis.
J. Org. Chem. 47, 374 (1982).
- V. J.O. Karlsson and T. Frejd
A comparison of the regioselectivity in the enol
acetate formation and the Vilsmeier-Haack reaction
of some methyl substituted cycloalkanones.
Manuscript.
- VI. T. Frejd and J.O. Karlsson
Cyclisations with methacrylic acid in PPA.
On the synthesis of cyclopenta[b]thiophenones.
Tetrahedron 35, 2155 (1979).
- VII. J.O. Karlsson
Bromination of some heteroaromatic acyl compounds with
aqueous bromine/sodium acetate.
Synth. Comm. 11, 29 (1981).

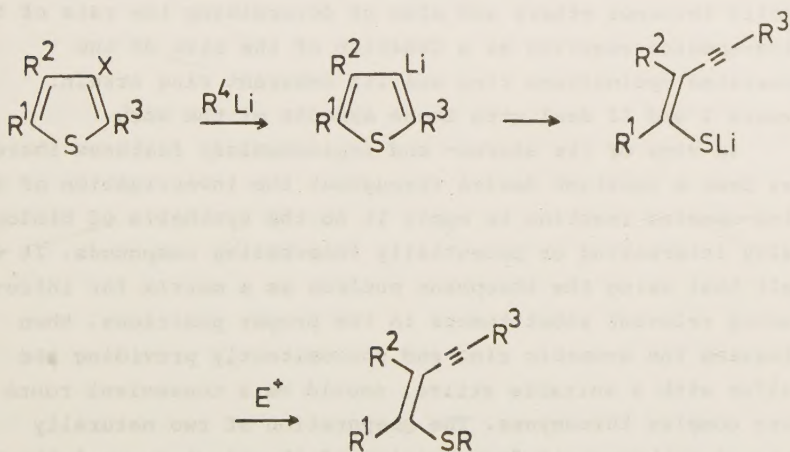
- VIII. J.O. Karlsson, S. Gronowitz and A. Hallberg
Organolithium-induced ring-opening of 3-halo-2,5-
dimethylthiophen-1,1-dioxides.
Acta Chem. Scand. B36, 341 (1982).
- IX. J.O. Karlsson, S. Gronowitz and A. Hallberg
Studies of the reaction of 2,5-disubstituted
3-bromothiophene-1,1-dioxides with some
organolithium reagents.
Chem. Scripta 20, 37 (1982).

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1. INTRODUCTION

The halogen-metal exchange reaction between β -halothiophenes and organolithium reagents represents a smooth and versatile method for introducing a variety of substituents in the thiophene β -position via the intermediate β -lithio derivatives, in agreement with established organolithium chemistry.¹ Care must be taken, however, that the reaction sequence be carried out at proper temperature. It is known that several β -thienyllithium derivatives rearrange to the thermodynamically more stable α -thienyllithium derivatives if one or both of the α -positions are unsubstituted or substituted with bromine.² These rearrangements are dominant at temperatures above -70°C . Moreover, in many cases the β -lithio derivatives have been found to suffer ring cleavage through a formal β -elimination at higher temperatures.^{3,4} The lithium thiolates formed can be trapped by electrophiles to yield thioenynes with a defined stereo- and regiochemistry³ (Scheme I).



Scheme I

Scattered reports about ring-opening reactions of the same type for other 5-membered aromatic heterocycles have appeared in the literature since 1891,³ when Claisen and Stock discovered the ring cleavage of 5-phenylisoxazole by sodium ethoxide.⁵ It was not until the late 1960's that chemists became interested in this type of reaction from a synthetic point of view. Extensive investigations have since been carried out in these laboratories on the scope and limitations of the ring-opening of 3-thienyl- and 3-selenienyllithium derivatives.^{3,4} The influence of various substituents on the heterocycle has been the major topic. In essence, it was found that -I-substituents in the 2-position decrease the rate of the reaction or make it not proceed at all, e.g. methoxy or chlorine groups, whereas +I-substituents such as alkyl groups favour the reaction. Exceptions to these generalizations are known. Perhaps the most stunning is the fact that 2,4-dimethoxy-3-lithiothiophene^{4a} and 2-chloro-3-lithio-5-methoxythiophene^{4b} both ring-open at room temperature.

The aim of this work has been to continue and extend the investigation started in these laboratories to bicyclic thiophene derivatives such as cycloalkane[b]thiophenes. Special emphasis was laid on the regiospecific synthesis of cyclic thioenol ethers and also of determining the rate of the ring-opening reaction as a function of the size of the annelated cycloalkane ring and its inherent ring strain. Papers I and II deal with these aspects of the work.

In view of its stereo- and regiochemical features there has been a constant desire throughout the investigation of the ring-opening reaction to apply it to the synthesis of biologically interesting or potentially interesting compounds. It was felt that using the thiophene nucleus as a matrix for introducing relevant substituents in the proper positions, then cleaving the aromatic ring and concomitantly providing the sulfur with a suitable attire, should be a convenient route to more complex thioenynes. The preparation of two naturally occurring thioenynes from species of the plant genus *Anthemis* was considered ample testing ground for the reaction. Paper III describes the successful synthesis of these compounds.

Certain synthetic problems in connection with these projects have been the subject of some further investigations during the course of the work, and are presented in Papers IV-VII.

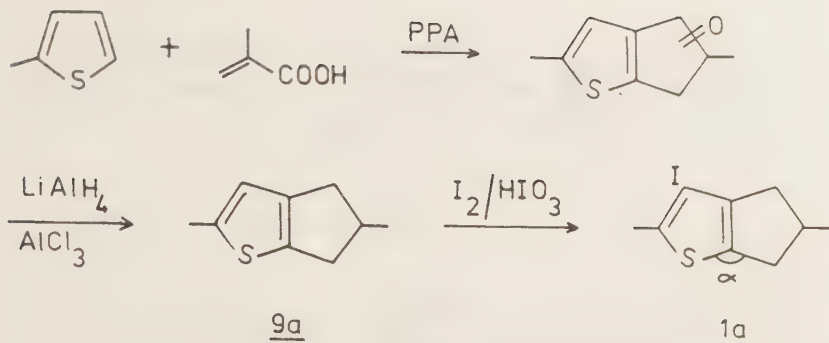
Finally, the examination of the behaviour of thiophene-1,1-dioxides towards organolithium reagents is described in Papers VIII and IX. The dioxides differ from the thiophenes in that they are not aromatic.

2. SYNTHESIS OF CYCLIC THIOENOL ETHERS

The regiospecific construction of substituted cycloalkane and cycloalkene derivatives has been and still is the focal point of much effort and brilliant ingenuity. Innumerable papers have dealt with this problem over the years, and many synthetic methods have been developed for that purpose. The resulting substances have been used for various purposes, be it as synthetic intermediates or target molecules - many natural products contain alicyclic structures - or as probes for theoretical investigations.

Thioenol ethers have gained increased attention due to their potential use as basic synthetic building blocks. Takei et al.⁶ and Wenkert et al.⁷ have successfully carried out transition-metal (Ni(O)) -catalyzed reactions with Grignard reagents on alkyl or aryl thioenol ethers, thereby replacing the alkyl- or arylthio groups with carbon-carbon bonds. Furthermore, Trost and Tanigawa have shown cyclic thioenol ethers to be allylically acetoxylated with palladium acetate. The ethers were subsequently treated with organocuprates to form new carbon-carbon bonds.^{8a} In addition, the same authors have demonstrated thioenol ethers to be regiospecifically phenylated in palladium-catalyzed reactions.^{8b}

The ring opening of bicyclic 3-iodothiophene derivatives which could conceivably yield cyclic 2-(1-propynyl)thioenol ethers was studied with special attention to regiospecificity (Paper I). The starting materials were synthesized by essentially known methods according to Schemes II-IV. The first step in the synthesis of 1a (Scheme II) is described in Paper VI. It should be noted that 1a is regiospecifically methylated at the 5-position.

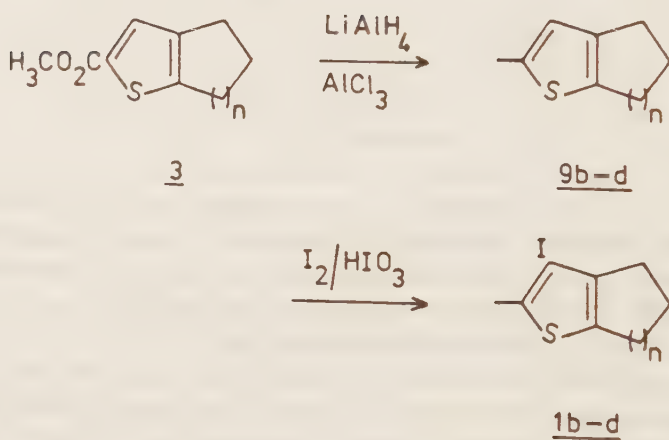
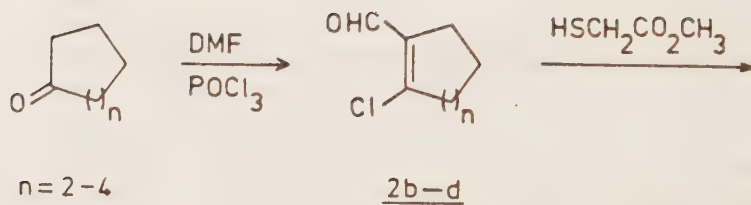


Scheme II

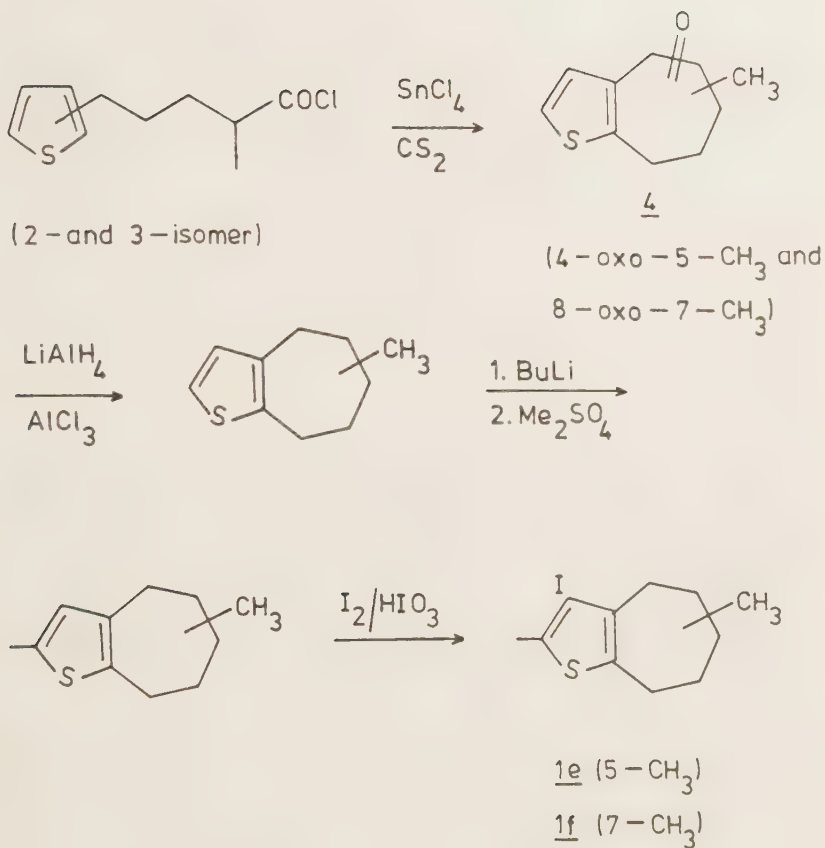
Compounds 1b-d, carrying no substituent in the annelated ring, were obtained from the corresponding cycloalkanones via the β -chlorovinyl aldehydes 2b-d,⁹ and subsequent Fiebelmann cyclizations afforded the thiophene esters 3,¹⁰ which were further elaborated to give 1b-d (Scheme III).

The methylcyclohepta[b]thiophenones 4 (Scheme IV) were prepared according to Cagniant et al.,¹¹ and were transformed to the isomerically pure 1e and 1f as indicated by capillary GC.

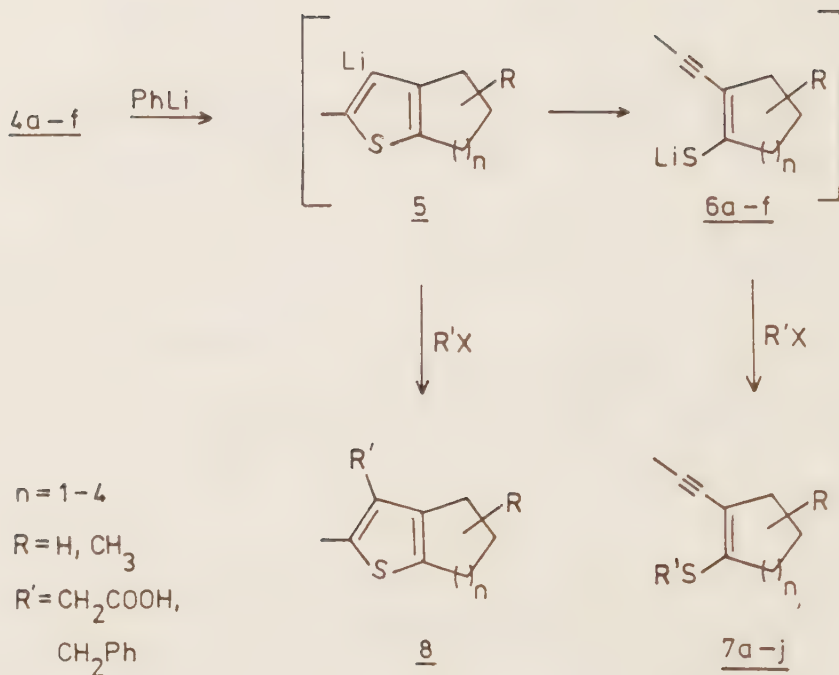
The compounds 1a-f were treated with phenyllithium in dry ether at room temperature. The 3-lithio derivatives 5 formed in the halogen-metal exchange reaction ring-opened spontaneously to the enyne thiolates 6a-f (Scheme V). Treatment of 6a-f with benzyl chloride or 6a-d with ethyl bromoacetate and subsequent hydrolysis of the esters resulted in the formation of the thioenol ethers 7a-j in 44-64 % yield. Thus, by using the thiophene nucleus as a matrix for substitution and cyclization reactions at an early stage in the reaction sequences, 7a, 7c and 7f and the S-acetic acid 7g could be obtained free of isomers in useful yields. This type of substances would be quite difficult to prepare by other routes, and this aspect of the ring-opening reaction is well suited for further development.



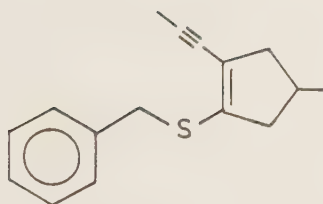
Scheme III



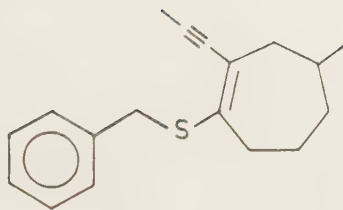
Scheme IV



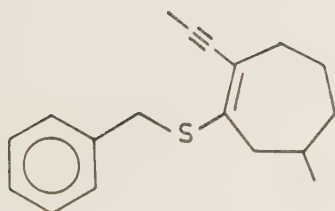
Scheme V



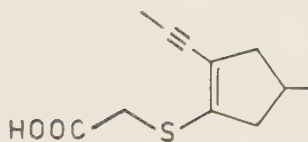
7a



7e



7f



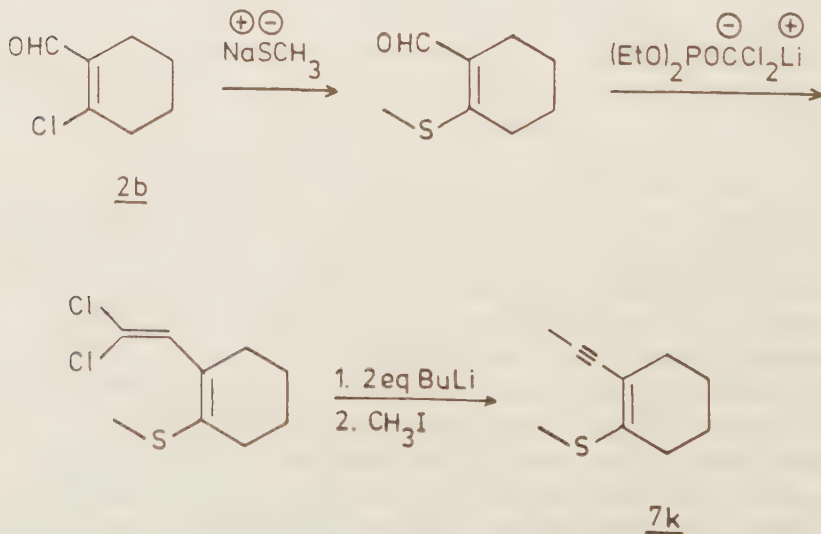
7g

The establishment of the enyne structures of these substances was not altogether trivial. It was necessary to find a method for safe distinction between the enynes and the isomeric thiophenes 8, which could possibly be formed, especially if the ring-opening reactions were slow.⁵³ The carbon-carbon triple bond absorptions were very weak in the IR spectra of the enynes. The ¹H NMR spectra were also not very useful for structural elucidation, apart from the appearance of the thienylic and propargylic methyl signals at somewhat different shifts, 2.3 ppm and 2.0 ppm, respectively. On the other hand, the mass spectra and above all the ¹³C NMR spectra proved to be most useful. The resonances of the

acetylenic carbons appeared in two distinct regions, 91.6-93.4 ppm and 76.0-81.4 ppm, clearly separated from the signals from the thiophene carbons of 9a-d, appearing at fields lower than 120 ppm. Introduction of a benzyl or an acetic acid substituent into the 3-positions of 9a-d should shift the resonance of the 3-carbons further downfield.¹² Additionally, the signals of the propargylic methyl carbons and the corresponding thienylic methyl carbons are sufficiently separated to make ¹³C NMR spectroscopy the method of choice for solving the structural problems in this investigation.

An alternative method for the preparation of cyclic thioenol ethers starting from the β -chlorovinyl aldehydes 2 is exemplified for the synthesis of 7k (Scheme VI). Thiolate substitution of 2b followed by a Wittig-Horner reaction and subsequent elimination and alkylation¹³ gave 7k in 22 % yield from 2b. This sequence constitutes a shorter route to the unsubstituted thioenol ether but does not seem to give the possibility of complete regiochemical control.

A more extensive study of the regiochemistry of the Vilsmeier-Haack reaction of unsymmetrical cycloalkanones was carried out (Paper V).

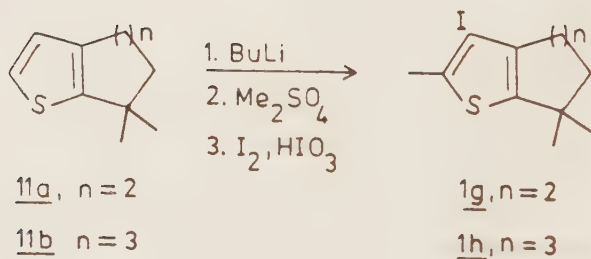
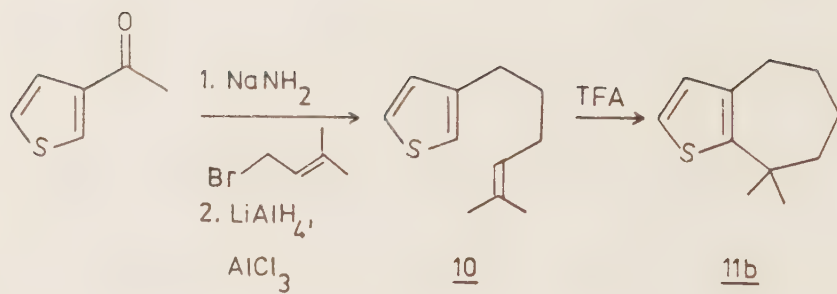


Scheme VI

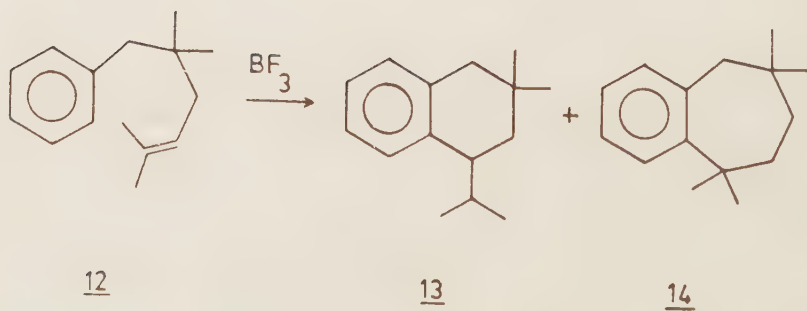
3. RING-OPENING RATES OF CYCLOALKANE[b] ANNELATED 3-THIENYLLITHIUM DERIVATIVES

During the ring-opening experiments described in Paper I, it was clear that the lithio thiophenes derived from 1a-b, i.e. the cyclopentane- and tetrahydrobenzo-annelated systems, ring-opened much faster than the others. In particular, the cycloheptane-annelated system seemed to be slow.

The reasons for this can be due to greater ring strain than in the cycloheptane and cyclooctane systems. Also, the angle α (see Scheme II) decreases upon ring cleavage, i.e. the sulfur atom approaches the adjacent thenylic carbon and its protons.¹⁴ There are indications in the literature that in the cycloheptane-annelated system, one of the protons on the thenylic carbon may be coplanar with the aromatic ring,¹⁵ i.e. that the sulfur atom and the proton are eclipsed. In order to estimate the influence of larger substituents on the thenylic carbon on the rate of ring opening (Paper II), the tetrahydrobenzo- and cycloheptane-annelated compounds 1g and 1h were synthesized from 11a¹⁶ and 11b (Scheme VII). Compound 11b was prepared from 3-acetylthiophene via alkylation with prenyl bromide, reduction and acid-promoted cyclization. The cyclization of 10 leaves the impression that the ring strain in the tetrahydrobenzo system is not negligible. Protonation of the double bond of 10 can occur at both carbons, and cyclization could lead to two products of different ring size. Cyclization of the benzene derivative 12 with boron trifluoride leads to a mixture of the benzocycloheptane 13 and the tetrahydronaphthalene 14 in a 1:2 ratio (Scheme VIII).¹⁷ However, cyclization of 10 led exclusively to 11b.



Scheme VII



Scheme VIII

The iodothiophenes 1a-d and 15, which has no additional ring strain, were treated with phenyllithium in ether at 2°C and trapped with dimethyl sulfate after various lengths of time (Scheme IX). The half-times for the ring-opening reactions were determined by measuring (GC) the amounts of 7 and 8, and 16 and 17. The halogen-metal exchange was complete in less than 10 s. Also, we assume that the reaction of 5 and 6 with dimethyl sulfate is very rapid and does not influence the half-time values to any great extent. The values are summarized in Table I:

Table I: Half-times for the ring-opening reactions of cycloalkane[b]-annelated thiophenes at 2°C

Starting material	Half-time
<u>1a</u>	< 5 s
<u>1b</u>	35 min
<u>1c</u>	8.5 h
<u>1d</u>	2.3 h
<u>1g</u>	52 h
<u>1h</u>	∞
<u>15</u>	3.3 h

The cyclopentane system, 1a, opens extremely rapidly, probably the result of substantial ring strain. The halogen-metal exchange and the ring opening were both complete within 10 s. The rates of ring opening of 1b-d and 15 are roughly of the same order of magnitude with 1b and 1c as the extremes. The explanations may be those mentioned above; a small amount of ring strain in 1b and the presence of a proton interacting with the sulfur atom in the opening of 1c.

The steric interactions were more serious when the protons on the thenylic carbon close to the sulfur were replaced with methyl groups. Thus, 1h gave no ring-opening products even at room temperature after 24 h, whereas 1g ring-opened completely in less than 15 h at the same temperature, to be compared with the half-times for the ring opening of 1b and 1c at 2°C, which were 35 min and 8.5 h, respectively.

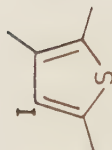
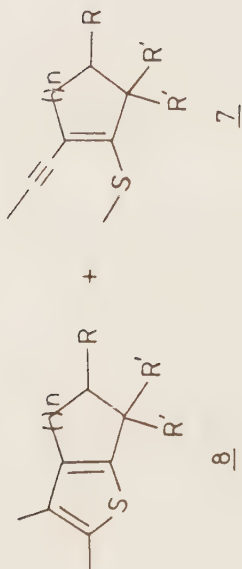
1a-d, g, h



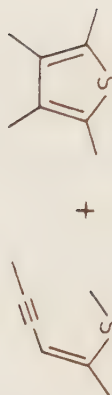
$n = 1-4$

$R = \text{H}, \text{CH}_3$

$R' = \text{H}, \text{CH}_3$



15



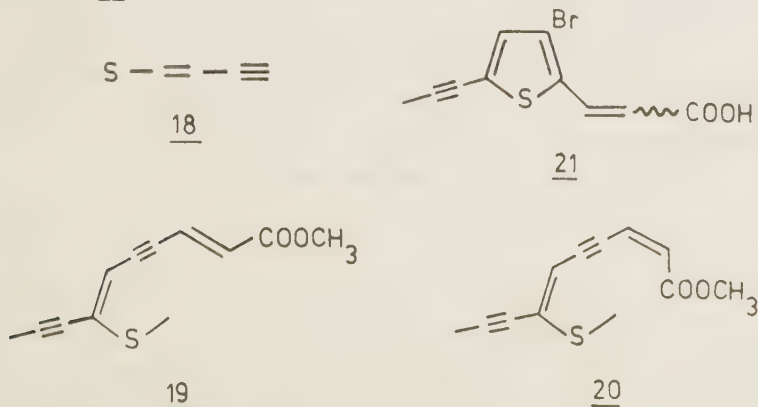
Scheme IX

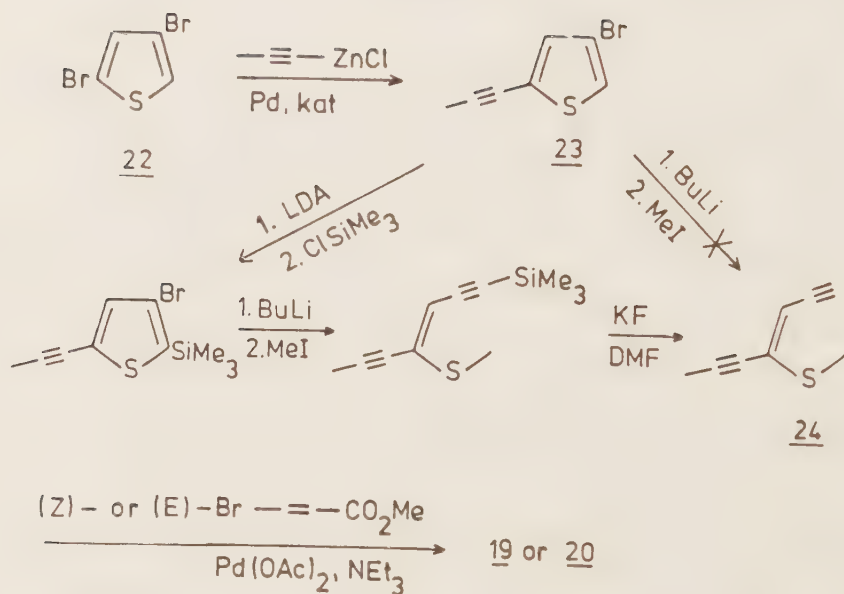
4. ACETYLENIC THIOENOL ETHERS FROM THE GENUS ANTHEMIS

Among the numerous polyacetylenes isolated from natural sources, especially from the family Compositae,¹⁸ several contain the thioenyn fragment 18 with cis as well as trans geometry around the double bond. Thus it was found by Bohlman and Skuballa¹⁹ that plants of the genus Anthemis are especially rich in this type of compounds, such as 19 and 20. They appeared to be particularly interesting target molecules for total syntheses based on the regio- and stereospecificity of the ring-opening reaction (Paper IV). This was further emphasized in view of the interesting biological effects that several polyacetylenic compounds are claimed to exhibit.¹⁸

Compounds 19 and 20 have previously been prepared by Bohlmann and Skuballa in a nonstereospecific synthesis, although in very low total yields,¹⁹ making biological testing impossible due to scarcity of material.

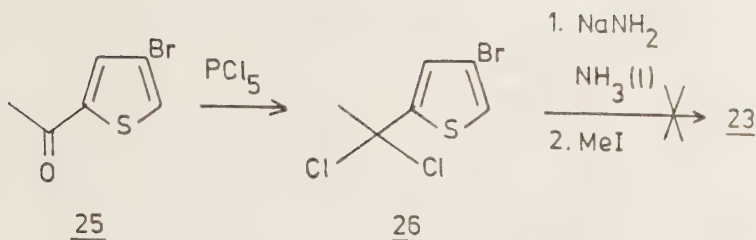
The ring opening of the cis- and trans-thiopheneacrylic acids 21 which would be an attractive route to 19 and 20 proved impracticable and attention was turned to their precursor 23 as a suitable key intermediate. Preparation of 23 was best achieved using a palladium-catalyzed coupling reaction²⁰ between propynylzinc chloride and 2,4-dibromothiophene 22 (Scheme X).





Scheme X

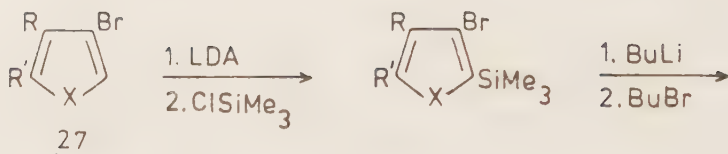
It can be mentioned that transformation of 2-acetyl-4-bromo-
 thiophene 25 into 23, analogous to the preparation of 2-propynyl-
 thiophene by Skattebøl in the synthesis of junipal,²¹ using the
 method of Vaitiekunas and Nord,²² produced a host of products
 together with intractable tars (Scheme XI). This can tentatively
 be explained by a metallation of the free α -position of 26 and
 subsequent reaction with the thenylic chloride moiety of
 another molecule resulting in polymerization.



Scheme XI

Ring opening of 23 would lead to the thioenyne 24 after S-methylation with methyl iodide. However, this approach failed to give any ring-opened product, and instead a number of different thiophene derivatives was obtained. Therefore, a general method for making terminal acetylenic thio- and seleno-enol ethers had to be developed (Paper V):

It has been found by Gronowitz and Frejd²³ and Jakobsen²⁴ that 3-thienyllithium derivatives with a free 2-position open quite slowly. On the other hand, +I-substituents such as alkyls increase the rate of ring opening.² Thus, we argued that a trimethylsilyl group in the 2-position might serve the same purpose. Since this group has proved to be easily displaced from acetylenic positions by potassium fluoride in N,N-dimethylformamide,²⁵ it seemed an ideal choice as promoter of the ring opening. The results obtained confirmed our anticipations and the reaction sequence is summarized in Scheme XII.



X = S; R, R' = H, CH₃

X = Se; R = R' = H



Scheme XII

The trimethylsilyl group was smoothly introduced via the 2-lithio derivatives of the heterocycles 27. Ring opening now proceeded effectively and desilylation was achieved according to the literature.²⁵ Overall yields of 28 were in the range of 30 %.

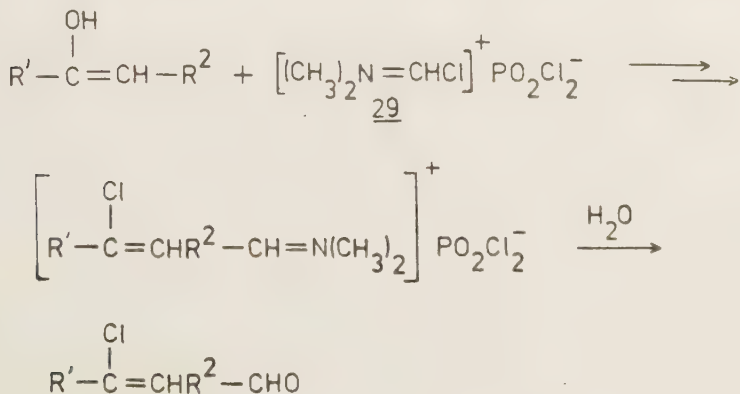
Compound 23 was treated accordingly to give 24 (Paper IV; Scheme X). The syntheses were then completed in one step by a palladium-catalyzed Heck coupling reaction between 24 and E- and Z-methyl-3-bromoacrylate²⁶ leading to 19 and 20, respectively in an overall yield of 17 % of each based on 2,4-dibromothiophene 22.

Compounds 19 and 20 have been tested in the Ames' test and were found inactive. Compound 19 has further been tested for antibacterial activity by Astra Läkemedel AB. The results were negative. The question remains, however, whether any of the compounds possesses any antikalsson activity.

5. REGIOCHEMISTRY OF THE VILSMEIER-HAACK REACTION

β -Chlorovinyl aldehydes, which can be obtained from ketones via the Vilsmeier-Haack reaction (cf. Scheme III) lend themselves to a variety of useful elaborations.²⁷

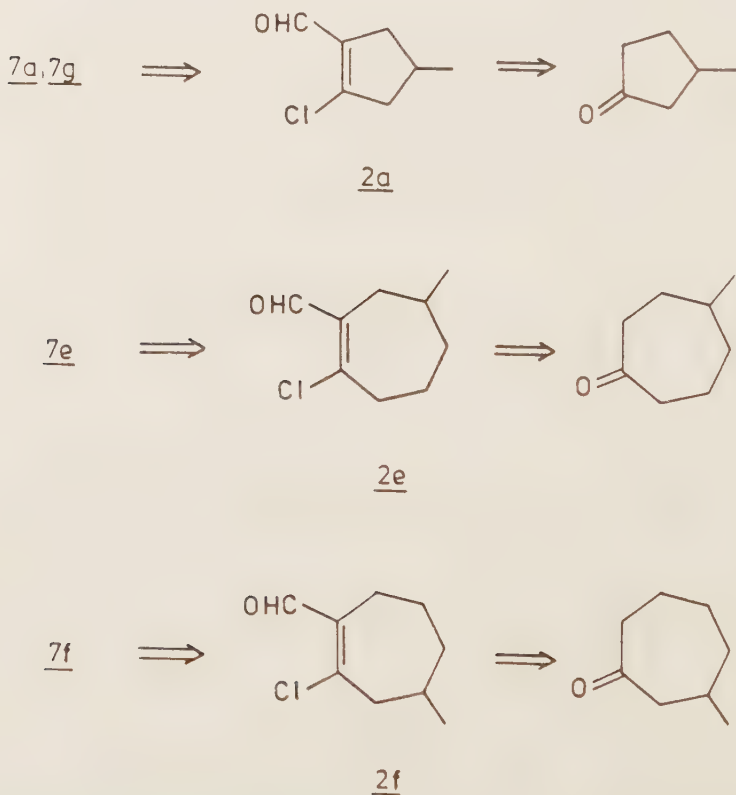
The mechanism of the Vilsmeier-Haack reaction is considered to involve a reaction between the enol of the ketone and the iminium species 29 generated from *N,N*-dimethylformamide and phosphoroxo chloride (Scheme XIII).²⁸ With unsymmetrical ketones there is an obvious possibility of obtaining a mixture of β -chlorovinyl aldehydes since two enols can be formed. Alkyl methyl ketones are known to give predominantly the compound with the formyl group at the internal α -carbon of the original ketone.²⁸ It has been shown, however, that steric bulk at the internal α -carbon can cause the other isomer to predominate, as is the case with 4-methyl-2-pentanone.²⁹



Scheme XIII

A number of cyclic β -chlorovinyl aldehydes has been prepared.^{27,28} Nevertheless, the problem of the regiochemistry of the Vilsmeier-Haack reaction on unsymmetrically substituted alicyclic ketones has not been much discussed.^{28,30}

We were interested in determining whether it would be possible to use suitably substituted methylcycloalkanones as starting materials for a regiospecific synthesis of the thioenol ethers 7a and 7e-g by the route outlined in Scheme VI. For this purpose we would need the β -chlorovinyl aldehydes 2a and 2e-f, which in turn should be derivable from the methylcycloalkanones depicted (Scheme XIV). The problem was whether the β -chlorovinyl aldehydes could be obtained free of the other conceivable isomers.

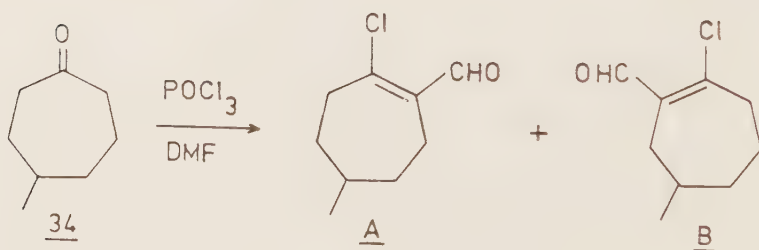
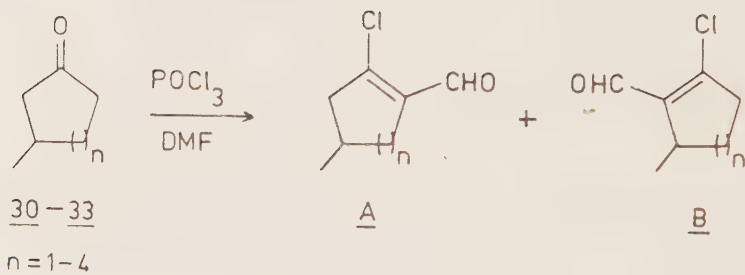


Scheme XIV

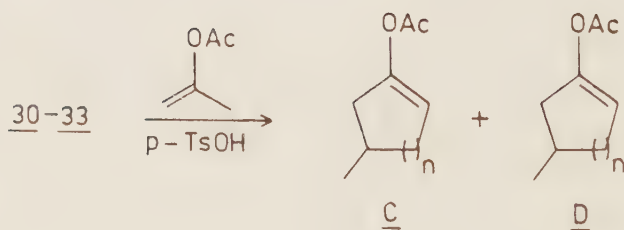
Since the Vilsmeier-Haack reagent is assumed to irreversibly attack a ring carbon of the cyclic enols, one would expect a steric interaction with the methyl group of one of the enols and the electrophile. This would lead to a more uneven distribution of the isomers as compared to e.g. in enol acetate formation. In the latter reaction the oxygen atom of the enols is attacked by the electrophile and consequently the steric interaction would be considerably less. We therefore compared the regiochemistry of the Vilsmeier-Haack reaction and enol acetate formation for some methyl-substituted cycloalkanones. This is described in Paper V (Schemes XV and XVI).

The methylcycloalkanones 30-34 were treated with a slight excess of DMF-POCl₃ (1.3/1.1) in trichloroethene at 55-60°C for 3 h for the Vilsmeier-Haack reaction,⁹ and with isopropenyl acetate as solvent and reagent with a catalytic amount of p-toluenesulfonic acid at 60-90°C for 15 h for enol acetate formation.³¹ Using trichloroethene as solvent in the latter reaction in the case of 31 did not change the situation, nor did the use of acetic anhydride as acylating agent with or without trichloroethene.³² We believe that the reaction conditions give thermodynamically controlled product compositions in both reactions. For instance, the enol acetate mixtures obtained from 32 and 33 did not change the ratio of isomers upon heating with 10 % p-toluenesulfonic acid at 120°C.³¹

The product distributions were determined (Tables II and III) by GC on crude products, together with ¹H NMR spectroscopy and shift reagents. In three of the cases in the Vilsmeier-Haack reaction there was a striking preference for the isomer with the formyl group distant from the methyl group. The isolated yields were all close to 50 %.



Scheme XV



Scheme XVI

Table II: Isomeric ratios A:B of the β -chlorovinyl aldehydes

Starting material	Ratio A:B
<u>30</u>	60:40
<u>31</u>	90:10
<u>32</u>	95:5
<u>33</u>	100:0
<u>34</u>	50:50

Table III: Isomeric ratios C:D of the enol acetates

Starting material	Ratio C:D
<u>30</u>	49:51
<u>31</u>	60:40
<u>32</u>	62:38
<u>33</u>	62:38

The results clearly show that the ketones which yield β -chlorovinyl aldehydes in a high isomeric ratio also give enol acetate mixtures in which the isomers with the double bond distant from the methyl group predominate. It is quite clear that the Vilsmeier-Haack reaction is more regioselective than enol acetate formation. Surprisingly, however, the seven- and eight-membered rings gave the highest isomer ratios of β -chlorovinyl aldehydes. One would have expected that the steric interactions between the electrophile and the methyl group of the enol would be considerably less in those cases than in the six- and above all the five-membered rings, due to greater flexibility of the larger rings.

Allylic strain is a well-known concept in cyclohexene systems³³ and we believe this to be a main reason for the preference of enol 35a over enol 35b. The methyl group of 3-methylcyclohexene has been shown to preferentially occupy a

pseudo-equatorial position,³⁴ and it seems reasonable that this is true for 35b as well. Thus, due to their partly eclipsed relationship, the allylic strain imposed between the methyl group and the adjacent proton in 35b should be larger than between the two protons in 35a (Figure 1).

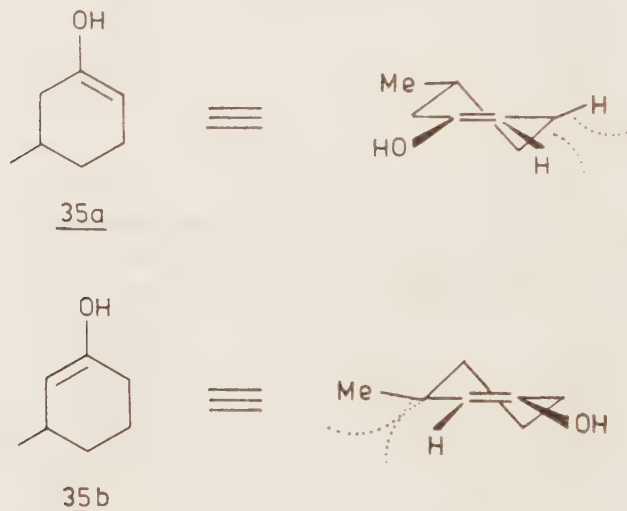


Figure 1

By studying Dreiding molecular models of the conceivable conformations of the enols of 32 and 33, the same kind of allylic strain seemed to be present as in the cyclohexene system, but other interactions in other parts of the rings may well be of greater importance for the explanation of the isomeric ratios obtained.

It seems reasonable that the high isomer ratios of β -chlorovinyl aldehydes can be interpreted to a certain extent by an unequal enol distribution, together with steric interactions between the electrophile and the methyl group of the enols.

Finally, it is obvious that none of 7a or 7e-g can be obtained completely regiospecifically via the Vilsmeier-Haack reaction. Nevertheless, the regioselectivity of the reactions on 31, 32 and 33 could be synthetically useful.

6. PPA-MEDIATED ANNELOTION OF METHACRYLIC ACID.
SYNTHESIS OF CYCLOPENTA[b]THIOPHENONES

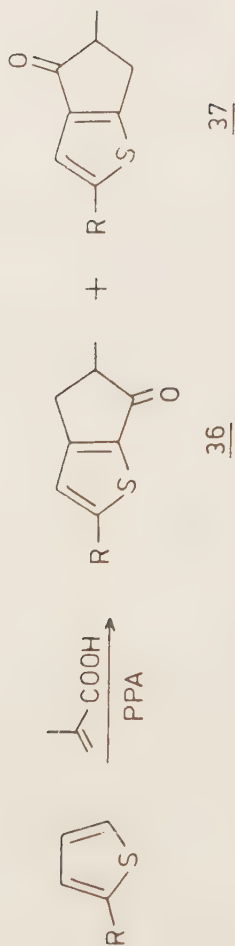
In connection with the synthesis of 1a we observed that the reaction between 2-methylthiophene and methacrylic acid in commercial polyphosphoric acid according to Meth-Cohn and Gronowitz³⁵ resulted in the formation of a mixture of isomers in a 70:30 ratio, but the yield was low (only 15 %).

On treating thiophene itself under the same conditions, only one product was formed.³⁵ Furthermore, it has been stated that methyl-substituted anisoles react with methacrylic acid in PPA to give products of only one isomer in each case.³⁶

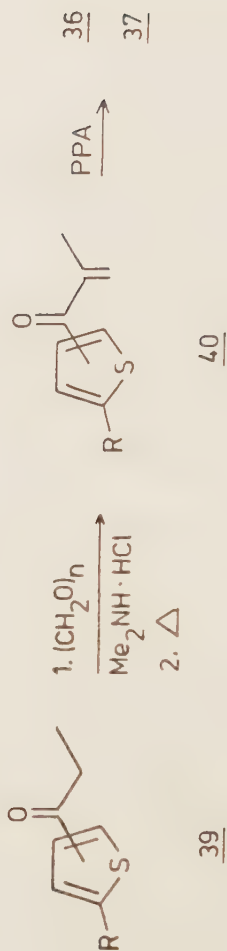
A number of 2-substituted thiophenes was treated with methacrylic acid in PPA (Scheme XVII). This is described in Paper VI. Yields and ratios of cyclized products are shown in Table IV.

Table IV: Isolated yields and ratios of 36:37

Starting material.	Yield	Ratio
R	%	<u>36:37</u>
H	7	99:1
Me	15	70:30
tBu	40	90:10
Ph	15	60:40
Cl	17	100:0
SMe	6	100:0



Scheme XVII



Scheme XVIII

Compounds 36 and 37 are probably formed via the thienyl-propanoic acids 38 formed by alkylation, and the α,β -unsaturated ketones 40 (the 2-isomers), formed by acylation of the thiophenes, followed by cyclization to the thiophene nucleus. This was substantiated by the presence of small amounts of some of these compounds in the reaction mixtures. The α,β -unsaturated ketones are easily cyclized in PPA, as evidenced in the syntheses of authentic samples (see below). Moreover, the 2-methylthienyl-propanoic acid 38 ($R = CH_3$) could be cyclized to 37a in PPA, but only after the addition of methacrylic acid. The assistance rendered by the methacrylic acid may be explained by its acidic properties, thereby changing the medium.

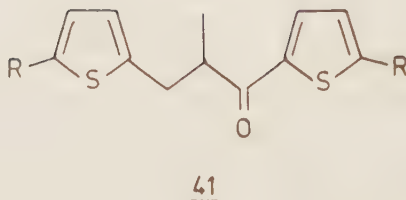
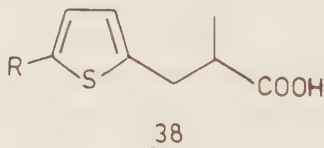
The intermediates 38 and 40 can furthermore be consumed in competitive reactions, e.g. to give ketones of type 41. Thus, a 26 % yield of 41 ($R = Cl$) was isolated from the cyclization reaction with 2-chlorothiophene. This makes us unable to generalize about the influence of the electronic properties of the substituents in the thiophenes on the ratios of cyclized products. Additionally, a great deal of polymer was formed in all experiments. It was shown that 2-methylthiophene was polymerized to the extent of 85 % in PPA at 50-60°C during 1 h, in the presence of even a catalytic amount of methacrylic acid. On the other hand, omission of the methacrylic acid left 85 % of the 2-methylthiophene intact under otherwise identical conditions.

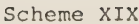
Authentic samples of 36 and 37 were prepared via 2- and 3-propionylthiophenes 39, respectively, followed by a Mannich reaction and thermal elimination of the dimethylammonium hydrochlorides to give the α,β -unsaturated ketones 40³⁵ (Scheme XVIII). Cyclization of these ketones in PPA gave the desired authentic samples.

It became necessary to confirm that the cyclization step proceeded without rearrangement, i.e. that the acyl group did not alter its point of attachment to the thiophene nucleus. Palmer et al.³⁷ stated that 3-(2-methyl-5-thienyl)propanoic acid 42 rearranged completely in PPA at 100°C to give the 6-one derivative 43 exclusively (Scheme XIX). We attempted to prepare 43 via cyclization of 44 in PPA. The compound formed was

different from that obtained from a repetition of the experiment of Palmer et al., but obviously isomeric with it.

The chemical shifts of the 3-C consistently appeared at 5-6 ppm higher field for compounds 37 than for compounds 36, and it was found that the shift of the 3-C of the compound obtained by Palmer et al. appeared at 5.9 ppm higher field than that of ours obtained from 44. This strongly suggested that the cyclization of 42 did not occur with rearrangement, and that Palmer et al. had obtained 45 instead. However, in order to rule out the possibility of all cyclizations having occurred with complete rearrangement, we measured the dipole moments of the tert.butyl derivatives 36c and 37c in benzene. These were found to be 4.6 ± 0.1 D and 3.5 ± 0.1 D, respectively, in agreement with the expected polarities, thus supporting our structural assignments. In conclusion, the compounds investigated do not rearrange upon cyclization in PPA under the conditions used.





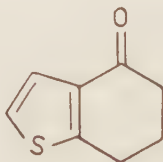
7. BROMINATION OF HETEROAROMATIC ACYL COMPOUNDS

Treatment of alkyl aryl ketones with bromine generally leads to formation of α -bromoketones,³⁸ i.e. the bromine enters into the side-chain. This occurs via an acid-catalyzed enolization by the hydrogen bromide formed and a subsequent fast bromination of the enol.³⁹ However, bromination of the aromatic nucleus can be achieved if the enolization is suppressed.

Pearson et al.⁴⁰ prepared several phenyl alkyl ketones, which were brominated in the phenyl ring by complexing the carbonyl group with excess aluminium chloride prior to addition of bromine. This has been called the "swamping catalyst effect". An additional feature of this effect is its strong meta-directing property due to the deactivation of the ortho and para positions of the complexed species. The method has proved useful also in the thiophene series,⁴¹⁻⁴³ and a number of experiments has shown the meta-directing effect to prevail, even when 2-acylthiophenes are subjected to the reaction.⁴¹ Thus, 2-acyl-4-bromothiophenes are produced despite the normally strong preference for electrophilic substitution to take place in the α -position.

Other ways of suppressing the acid-catalyzed enolization have been used with hydroxy- and methoxyacetophenones. These compounds are brominated in the aromatic nucleus by bromine in aqueous acetic acid⁴⁴⁻⁴⁶ or in anhydrous acetic acid containing alkali acetate. In contrast, side-chain bromination occurs in anhydrous acetic acid alone.^{47,48}

4,5,6,7-Tetrahydrobenzo[b]thiophen-4-one 46 has been brominated in the 2-position by bromine in aqueous acetic acid.⁴⁹



46

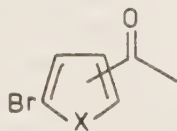
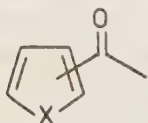
To our knowledge, no other report of the bromination of acylthiophenes in the presence of water or alkali acetate has appeared.

We treated some acylthiophenes and -selenophenes with bromine in aqueous sodium acetate or anhydrous acetic acid containing sodium acetate, depending on the solubility of the starting materials (Table V). This is described in Paper VII. The products were obtained in 55-75 % yield.

Table V: Results of the bromination reactions

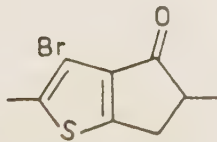
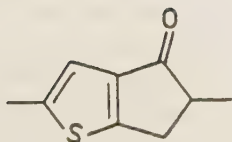
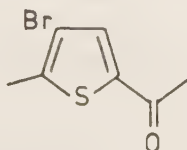
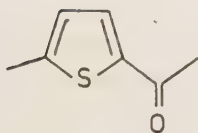
Starting materials

Products



X = S, Se
(2- and 3-isomers)

47



The acetylselenophenes behaved somewhat awkwardly in that the first equivalent of bromine was quickly decolourized when added to the reaction mixture. It turned out, however, that after aqueous work-up, considerable amounts of the starting materials remained, 30 % of the 3-acetylselenophene and 65 % of the 2-acetylselenophene. It was found in the former case that heating the reaction mixture to 90°C effected total consumption of the starting material. Heating the reaction mixture in the latter case did not change the situation, but addition of another equivalent of bromine brought about a complete monobromination. Addition of an extra equivalent of bromine to 3-acetylselenophene resulted in the formation of considerable amounts of dibrominated product.

These facts point to the possibility of bromine addition to the selenium atom, which has been mentioned earlier in the literature.^{50,51} The addition products are known to lose bromine on heating.⁵²

The formation of 2-acetyl-5-bromothiophene and -selenophene 47 (the 2-isomers) shows this method to be a complement to the aluminium trichloride-catalyzed method by which the 4-bromo derivatives are formed instead.^{41,42,53}

8. RING CLEAVAGE OF 3-HALOTHIOPHENE-1,1-DIOXIDES

During an investigation of the chemistry of thiophene-1,1-dioxides it was found that treatment of 3-bromothiophene-1,1-dioxide 48 with one equivalent of butyllithium in ether at -70°C produced a 61 % yield (GC) of butyl bromide via a halogen-metal exchange reaction. The intermediate lithio derivative 50 could be trapped neither with carbon dioxide to give the corresponding carboxylic acid nor with methanol to give the dehalogenated compound. Instead, refluxing the crude product with benzyl bromide in methanol produced the enynic sulfone 52 in 14 % yield (GC). Its structure was confirmed by an independent synthesis by oxidizing the corresponding sulfide 53⁵³ with m-chloroperbenzoic acid.

Additionally, the reaction product contained components with acetylenic structures according to IR spectroscopy. GC-MS suggested the presence of two isomers in a 1.0:1.7 ratio with a molecular weight equal to the carbon skeleton of the starting material plus one butyl group. Much of the starting material remained, but was completely consumed if two equivalents of butyllithium were used. In addition, the yield of the two isomers mentioned above rose to a total of 35 % (GC). This is reported in Papers VIII and IX.

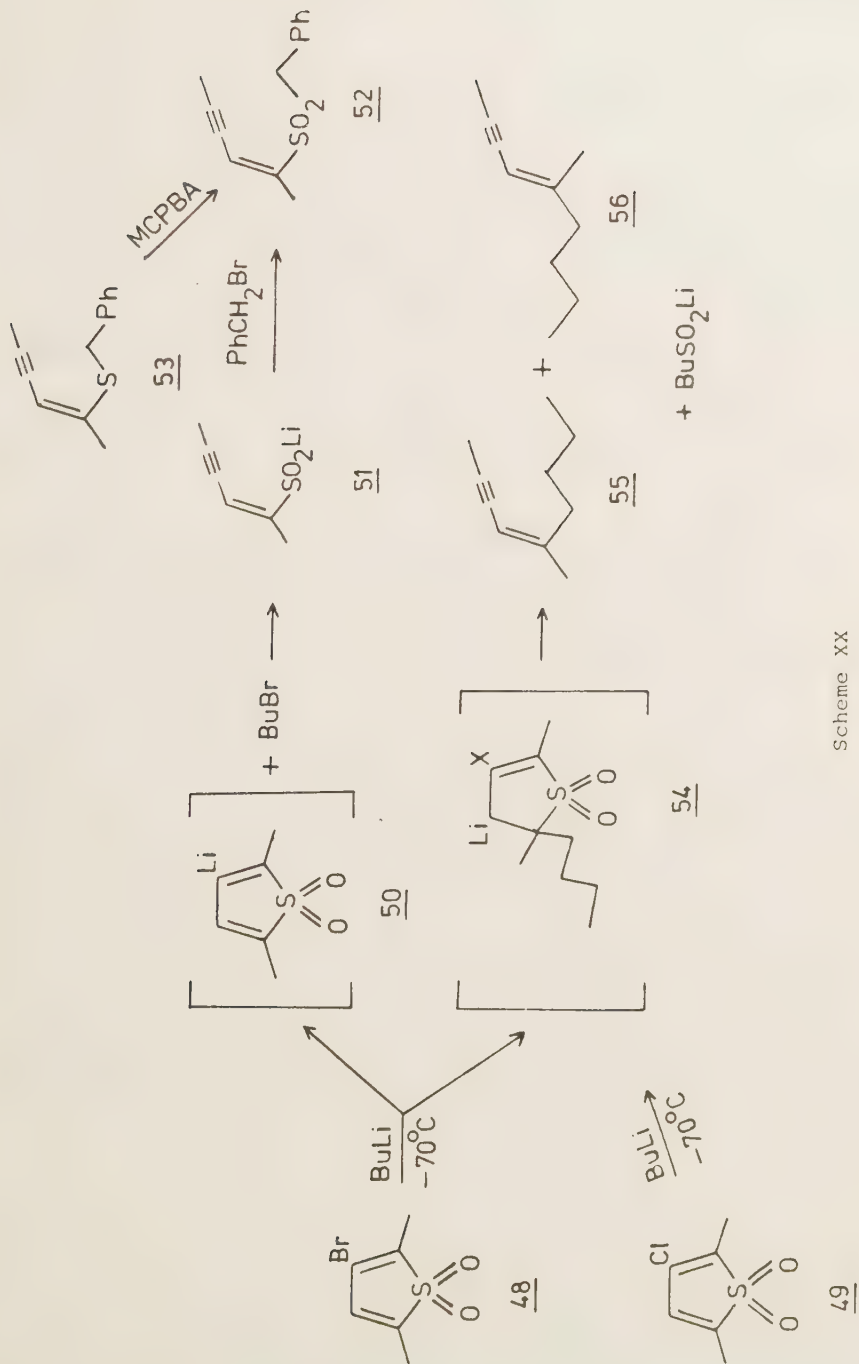
The isomers were isolated as a mixture, and their IR and ^1H NMR spectra, together with decoupling experiments, as well as elemental analysis, showed their structures to be 55 and 56. The assignments of the configurations around the carbon-carbon double bond were primarily based on the expected anisotropy effect of the carbon-carbon triple bond. The methyl group resonating at lower field was assigned to be in the cis-position to the triple bond.

Treatment of 3-chloro-2,5-dimethylthiophene-1,1-dioxide 49 with two equivalents of butyllithium in ether at -70°C gave an 80 % yield (GC) of the enynes 55 and 56 in the same ratio as that observed on starting from 48. No butyl chloride could be found.

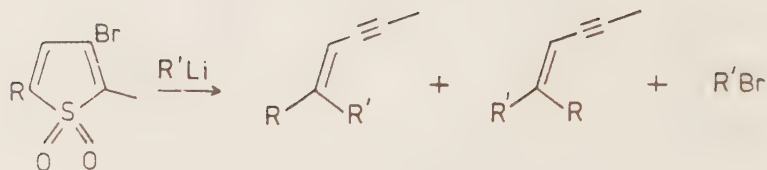
We assume that the different products were formed via two different pathways (Scheme XX), both implying a ring cleavage:

- a) halogen-metal exchange to produce the 3-lithio derivative 50, which then undergoes a rapid internal β -elimination of lithium sulfinate producing the enynic sulfinate 51, which was benzylated to give 52. The low yield of 52 compared to the amount of butyl bromide formed might be explained by polymerization during alkylation.⁵⁴
- b) butyllithium attack at the 5-carbon of 48 to give the intermediate 54, which rapidly equilibrates, and then ring opening leads to 55 and 56 with elimination of lithium bromide and sulfur dioxide in either a concerted or stepwise process. The sulfur dioxide should be trapped by butyllithium to give butyl sulfinate, which would explain the need of an excess of butyllithium. No benzylbutyl sulfone could be detected in the crude product after benzylation, but on the other hand, alkylsulfonates are known to be readily polymerized.⁵⁵

A number of 5-substituted 3-bromo-2-methylthiophene-1,1-dioxides 57 were treated with various organolithium reagents (Scheme XXI). The results can be summarized in the following way. The larger isopropyl and tert-butyl groups of 57c and 57e hindered the attack of n-butyl and t-butyllithium considerably and the total GC yields of enyne mixtures ranged between 1 % and 8 %, while the amount of alkyl bromide formed was as high as 80 % in one case. Reaction of methyl-, ethyl-, n-butyl- and phenyllithium with 57a-b and 57d gave mixtures of enynes in 25-41 % yield (GC). The ratio of the enynes was also influenced by the 5-substituent of the thiophene dioxide in the sense that the large substituents more strongly preferred the trans-position to the carbon-carbon triple bond than the smaller. Furthermore, upon treatment of 57a-b and 57d with phenyllithium, an increase in the size of the 5-substituent from a methyl to an n-butyl group surprisingly resulted in an increasing amount of the enynes with the phenyl group cis to the triple bond. That phenyl group was found to be out of plane



Scheme XX



57a-e

$R = \text{Me, Et, } i\text{-Pr, } n\text{-Bu, } t\text{-Bu}$ a-e

$R' = \text{Me, Et, } n\text{-Bu, } t\text{-Bu, Ph}$

Scheme XXI

with the enyne system according to the ^1H NMR data. Yields of alkyl and phenyl bromides were in the range of 50-60 % (GC), roughly making up the material balance.

Further support for the proposed pathways was offered by the discovery of benzylphenyl sulfone after benzylation of the crude product when phenyllithium was allowed to react with 57a. This demonstrates that the organolithium reagent is partly consumed by trapping the sulfur dioxide moiety of the thiophene dioxide.

Treatment of 57a with n-butyllithium and 57d with methyl-lithium led to the same two enynes in identical ratios, strongly supporting the presence of a common intermediate such as 54.

It is interesting to note the different behaviour of organolithium reagents and nitrogen nucleophiles, which appear to give Michael additions to the thiophene dioxides by attacking the 3-position.^{56,57}

The similarity of the 3-lithio derivative 50 and many 3-lithiothiophenes concerning their ability to undergo ring opening is conspicuous. It must nevertheless be kept in mind that the 3-lithiothiophene dioxides are non-aromatic. The sulfinat anion is a very good leaving group and several examples of the β -elimination of sulfinates in aliphatic compounds have been reported.^{58,59} The 3-lithiothiophenes are aromatic, or at least are considered to be. The driving force for the ring cleavages may be of the same nature in both cases. Indeed, the very fact that the 3-lithiothiophenes ring-open is cause enough to call in question the degree of their aromaticity. A low resonance stability of 3-thienyllithium derivatives could partly explain their easy ring opening. Examples of thiolate eliminations in aliphatic systems are given in Refs. 59 and 60.

9. ACKNOWLEDGEMENTS

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10. REFERENCES

1. S. Gronowitz, *Adv. Heterocycl. Chem.* 1, 1 (1963).
- 2a. S. Gronowitz and P. Moses, *Ark. Kemi* 18, 119 (1961).
- 2b. S. Gronowitz and B. Holm, *Acta Chem. Scand.* 23, 2207 (1969).
3. S. Gronowitz and T. Frejd, *J. Heterocycl. Compd.*
(Engl. Transl.) 353 (1978).
- 4a. A. Hallberg, T. Frejd and S. Gronowitz,
J. Chem. Soc. Perkin Trans. I 1390 (1980).
- 4b. S. Gronowitz, A. Hallberg and T. Frejd,
Chem. Scripta 15, 1 (1980).
5. I. Claisen and R. Stock, *Chem. Ber.* 24, 130 (1891).
6. H. Okamura, M. Miura and H. Takei,
Tetrahedron Lett. 43 (1979).
7. E. Wenkert, T.W. Ferreira and E.L. Michelotti,
J. Chem. Soc., Chem. Commun. 637 (1979).
- 8a. B.M. Trost and Y. Tanigawa,
J. Am. Chem. Soc. 101, 4413 (1979).
- 8b. B.M. Trost and Y. Tanigawa, *ibid.* 101, 4743 (1979).
9. W. Ziegenbein and W. Lang, *Chem. Ber.* 93, 2743 (1960).
10. S. Hauptmann and E.-M. Werner,
J. Prakt. Chem. 314, 499 (1972).
11. P. Cagniant, G. Merle and D. Cagniant,
Bull. Soc. Chim. Fr. 322 (1970).
12. L. Zetta and G. Gatti, *Org. Magn. Reson.* 4, 585 (1972).
13. J. Villieras, P. Pierrot and J.F. Normant,
Synthesis 458 (1975).
14. T. Frejd, Thesis, Lund 1975.
15. N.L. Allinger and J.T. Sprague,
J. Am. Chem. Soc. 94, 5743 (1972).
16. A. Corvers, J.H. van Mil, M.M.E. Sap and H.M. Buck,
Recl. Trav. Chim. Pays-Bas 96, 18 (1977).
17. H. Hart and J.L. Corbin,
J. Am. Chem. Soc. 87, 3135 (1965).
18. F. Bohlmann, T. Burkhardt and C. Zdero,
"Naturally Occurring Acetylenes", p. 381,
Academic Press, New York 1973.

19. F. Bohlmann and W. Skuballa, Chem. Ber. 103, 1886 (1970).
20. A.O. King and E. Negishi, J. Org. Chem. 43, 358 (1978).
21. L. Skatteböl, Acta Chem. Scand. 13, 1460 (1959).
22. A. Vaitiekunas and F.F. Nord,
J. Am. Chem. Soc. 76, 902 (1954).
23. S. Gronowitz and T. Frejd,
Int. J. Sulfur Chem. A2, 165 (1972).
24. H.-J. Jakobsen, Acta Chem. Scand. 24, 2663 (1970).
25. E.J. Corey and R.A. Ruden, Tetrahedron Lett. 1495 (1973).
26. J.R. Weis, B.A. Patel and R.F. Heck,
J. Org. Chem. 45, 4926 (1980).
27. M. Pulst and M. Weissenfels, Z. Chem. 16, 337 (1976).
28. C. Jutz, Adv. Org. Chem. 9(1), 274-285 (1976).
29. H. Schellhorn, S. Hauptmann and H. Frischleder,
Z. Chem. 13, 175 (1973).
30. B. Hesse, R. Moll and A. Hantschmann,
Z. Chem. 12, 136 (1972).
31. H.O. House and V. Kramar, J. Org. Chem. 28, 3362 (1963).
32. G. Descotes and Y. Querou, Bull. Soc. Chim. Fr. 3395 (1968).
33. F. Johnson, Chem. Rev. 68, 375 (1968).
34. J. Lessard, P.V.M. Tan, R. Martino and J.K. Saunders,
Can. J. Chem. 55, 1015 (1977).
35. O. Meth-Cohn and S. Gronowitz,
Acta Chem. Scand. 20, 1577 (1966).
36. J.R. Merchant, M.S. Kamath and S.T. Dike,
J. Chem. Soc. Perkin Trans. I 2089 (1977).
37. M.H. Palmer, D.S. Leitch and C.W. Greenhalgh,
Tetrahedron 34, 1015 (1978).
38. H.O. House, "Modern Synthetic Reactions", 2nd ed.,
pp. 459-478. W.A. Benjamin, Inc., New York, 1972.
39. L.P. Hammett, "Physical Organic Chemistry", 2nd ed.,
pp. 96-99. McGraw-Hill Book Company, New York, 1970.
40. D.E. Pearson and H.W. Pope, J. Org. Chem. 21, 381 (1956).
41. Ya.L. Goldfarb, Yu.B. Volkenstein and L.I. Belenkii,
Angew. Chem. 80, 547 (1968) and references cited therein.
42. R. Lantz and A.-B. Hörnfeldt, Chem. Scripta 2, 9 (1972).
43. B.-P. Rogues, M.-C. Fournie-Zaluski and R. Oberlin,
Bull. Soc. Chim. Fr. 2334 (1975)

44. H.M. Priestley and E. Moness, J. Org. Chem. 5, 358 (1940).
45. Ng.Ph. Buu-Hoi, Ng.D. Xuong and D. Lavit,
J. Chem. Soc. 1034 (1954).
46. Ng.Ph. Buu-Hoi and D. Lavit, J. Chem. Soc. 18 (1955).
47. F. Kröhnke and K. Ellegast, Chem. Ber. 86, 1556 (1953).
48. K.N. Rosenmund and K. Pfroepffer,
Chem. Ber. 90, 1922 (1957).
49. S. Nishimura, M. Nakamura, M. Suzuki and E. Imoto,
J. Chem. Soc. Japan 83, 343 (1962);
D.T. Drewry and R.M. Scrowston,
J. Chem. Soc. (C) 2750 (1969).
50. H. Suginome and S. Umezawa,
Bull. Chem. Soc. Jpn 11, 157 (1936); C. A. 30, 5981 (1936).
51. V.P. Litvinov, Ya.L. Goldfarb and I.P. Konjaeva,
Izv. Akad. Nauk SSSR, Ser. Khim. 29, 372 (1980)
and references cited therein.
52. T.Q. Minh, L. Christiaens and M. Renson,
Bull. Soc. Chim. Fr. 2239 (1974).
53. S. Gronowitz and T. Frejd, Acta Chem. Scand. B30, 287 (1976).
54. E.V. Polunin, I.M. Zaks, A.M. Moiseenkov and A.V. Semenovskii,
Izv. Akad. Nauk SSSR, Ser. Khim. 28, 641 (1979).
55. P. Allen, Jr., J. Org. Chem. 7, 23 (1942).
56. W.J. Bailey and E.W. Cummins,
J. Am. Chem. Soc. 76, 1932 (1954).
57. J.P. Walsh, Diss. Abstr., Int. B. 31, 1846 (1970),
(with L.F. Hatch).
58. C.J.M. Stirling, Int. J. Sulfur Chem. B6, 277 (1971).
59. D.R. Marshall, P.J. Thomas and C.J.M. Stirling,
J. Chem. Soc. Chem. Comm. 940 (1975).
60. R.R. Schmidt and B. Schmid, Tetrahedron Lett. 3583 (1977).

